REMARKS/ARGUMENTS

Claims 63-66 and 68-70 are currently pending in the instant application.

I. Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 63-66 and 68-70 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 2 of the instant Office Action).

Claims 63-66 and 68-70 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 3 of the instant Office Action).

Applicants submit, as discussed below and in previous Responses of record, that not only has the PTO not established a *prima facie* case for lack of utility, but that the polypeptides of Claims 63-66 and 68-70 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without any further experimentation.

The gene amplification data disclosed in Example 114 establishes a credible, substantial and specific patentable utility for the PRO274 polypeptides.

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the claimed PRO274 polypeptides for the reasons previously set forth in Applicants' Responses filed on November 18, 2004, April 8, 2005, and October 28, 2005, in the Preliminary Amendment and Supplemental Preliminary Amendment filed July 10, 2006 and September 6, 2006 and the Response filed January 11, 2007.

Furthermore, as first discussed in Applicants' Response of November 18, 2004, Applicants rely on the gene amplification data for patentable utility of the PRO274 polypeptide, and the gene amplification data for the gene encoding the PRO274 polypeptide is clearly disclosed in the instant specification under Example 114. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO274 in at least three of the lung tumors listed in Table 9.

Table 9 teaches that the nucleic acids encoding PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold amplification or 2.0 fold to 3.05-fold amplification in three types of human primary lung tumors, LT4, LT16, and LT18.

As further support for their utility claim, Applicants have submitted a Declaration by Dr. Audrey Goddard (made of record in the Response submitted November 18, 2004), which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. According to the Goddard Declaration, the 2.0- to 3.05-fold amplification of the PRO274 gene in 3 different lung tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed therein. The Examiner has not provided any evidence to show that the disclosed DNA amplification is not significant.

Applicants have also submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in the Response submitted November 18, 2004) collectively teach that in general, gene amplification increases mRNA expression. Further, Applicants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis and Dr. Randy Scott (made of record in the Preliminary Amendment of July 10, 2006 and Supplemental Preliminary Amendment of September 6, 2006), which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the two Polakis Declarations, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably

expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed and has utility in the diagnosis of colon cancer.

The Examiner has asserted that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the PRO274 polypeptide would be useful diagnostically. The Examiner has acknowledged that the gene amplification assay provides a patentable utility for the PRO274 nucleic acid and that changes in level of mRNA correlate with changes in protein abundance. However, the Examiner asserts "the only issue remaining is whether gene amplification correlates with increased transcription and mRNA levels." (Page 3 of the instant Office Action). In support of this assertion, the Examiner refers to articles by Pennica *et al.*, Konopka *et al.*, Li et al and Godbout et al. as evidence showing "there is not always a such a correlation.".

A prima facie case of lack of utility has not been established

As a preliminary matter, Applicants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant.

Applicants further submit that it is not a legal requirement to establish that gene amplification "necessarily" or "always" results in increased expression at the mRNA and polypeptide levels, or that protein levels can be "accurately predicted." As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a

correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Pennica et al.

The Examiner cited the abstract of Pennica *et al.* for its disclosure that "WISP-1 gene amplification and overexpression in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner concluded that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty.

In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*" (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Thus the findings of Pennica *et al.* with respect to WISP-1 support Applicants' arguments. In the case of WISP-3, the authors report that there was no change in the DNA copy number, but there was a change in mRNA levels. This apparent lack of correlation between DNA and mRNA levels is not contrary to Applicants' assertion that a change in DNA copy number generally leads to a change in mRNA level. Applicants are not attempting to predict the DNA copy number based on changes in mRNA level, and Applicants have not asserted that the only means for changing the level of mRNA is to change the DNA copy number. Therefore a change in mRNA without a change in DNA copy number is not contrary to Applicants' assertions.

The fact that the single WISP-2 gene did not show the expected correlation of gene amplification with the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack of correlation observed for the WISP-2 gene is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, as was demonstrated for WISP-1.

Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Konopka et al.

The Examiner cited the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to gene amplification but to variation in the level of mRNA produced from a single genomic template." (Page 6 of the instant Office Action).

Applicants submit that the PTO has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al.*, Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . ." is not sufficient to establish a *prima facie* case of lack of utility. It is not enough to show that for a particular gene a correlation does not exist. The law requires that the Examiner show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made.

Li *et al.*

The Examiner also cites Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 3 of the instant Office Action). Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article

(of record), genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above the PRO274 gene showed 2.0 fold to 3.05-fold amplification in three different lung tumors, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO274, would be expected to show a corresponding increase in transcript expression.

Godbout *et al.*

The Examiner asserts that Godbout *et al.* teaches that "co-amplified genes are only over-expressed if they provide a selective growth advantage to the cells." (Page 5 of the instant Office Action). Applicants respectfully submit that the passage cited by the Examiner is based upon two references from 1987 and 1992. In contrast, Applicants have made of record three more recent references, published in 2002, by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Applicants' Response filed on November 18, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.*

The Examiner alleges that the instant specification does not teach structure/function analysis. The Examiner states that "[i]t is not disclosed, and based upon the sequence searches in this case, the Examiner cannot find any reason to suspect, that the protein encoded by the PRO274 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell." The Examiner also questions whether the level of genomic amplification of DDX1 gene is comparable to that of PRO274 (Pages 5-6 of instant Office Action).

First of all, Applicants submit that the cited reference, Godbout *et al.*, was presented as evidence to support the existence of a general correlation between genomic DNA amplification and protein expression. Applicants have asserted utility for PRO274 as a novel tumor marker based on its positive result in the gene amplification assay. Applicants respectfully submit that it was never claimed that PRO274 is similar in any way to the DDX1 gene of Godbout *et al.*, they never claimed PRO274 was an RNA helicase or that it confers selective advantage to cell survival; on the other hand, the Godbout reference was submitted to show good correlation between protein levels based upon genomic DNA amplification, which the Examiner clearly agrees with. Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer and structure/function data, which the Examiner requests, is not a requirement for the utility requirement. Hence a *prima facie* case has not been established and this rejection is improper.

On pages 5-6 of this rejection, the Examiner contemplates an explanation for how PRO274 "confer[s] a selective advantage to a tumor cell"; in other words, on the mechanism by which PRO274 acts. That is, rather than focusing on the positive result itself, the Examiner seems to focus on the mechanism of action. However, knowledge of the mechanism is not relevant, nor required for the claimed invention to be useful. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)."

Moreover, as the Examiner is aware, there are many pathways to tumorigenesis, and screening for novel diagnostic tumor markers is routine in the art. Even for the identification a tumor marker, a showing of homology to other known tumor proteins (like RNA helicase) is not required. For this additional reason, the Examiner's concerns are misplaced, and should be withdrawn.

In summary, Applicants respectfully submit that the Examiner has not shown that a change in gene amplification level in tumor as compared to normal tissue is not correlated with a change in mRNA and hence protein expression. The Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica *et al.*, Konopka *et al.*, Li *et al.* and Godbout *et al.* articles do not provide sufficient reasons to doubt the statements by Applicants that PRO274 has utility. As discussed above, the law does not require that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed November 18, 2004) collectively teach that in general, gene amplification increases mRNA expression.

Second, Applicants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis with their Preliminary Amendment filed on July 10, 2006, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Third, Applicants would like to bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9 of the Decision). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the

PRO274 polypeptide to refute Applicants' assertion of a correlation between mRNA levels and protein expression.

Thus, taken together, all of the submitted evidence supports Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. Applicants further submit that the Examiner has not presented any evidence specific to the PRO274 polypeptide to refute Applicants' assertion of a correlation between gene amplification levels and mRNA and protein expression.

Applicants maintain that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the mRNA transcript will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, vol. 1, pages 37-45 - made of record in the Response submitted November 18, 2004) studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract).

In addition, Hyman *et al.* (*Cancer Res.*, 2002, vol. 62, pages 6240-45 - made of record in the Response submitted November 18, 2004) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph).

Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, vol. 99, pages 12963-12968 -made of record in the Response submitted November 18, 2004) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels."

Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Taken together, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declarations, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO274 polypeptide and the claimed antibodies that bind it have utility in the diagnosis of cancer.

Accordingly, Applicants respectfully request reconsideration and reversal of the rejections of Claims 63-66 and 68-70 under 35 U.S.C. §101.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Although no fees are due, the Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2630 P1C8**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 19, 2007

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